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Adjuvant Chemotherapy of Childhood Posterior Fossa Ependymoma: Cranio-Spinal Irradiation With or Without Adjuvant CCNU, Vincristine, and Prednisone: A Childrens Cancer Group Study

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In 1975, members of The Children's Cancer Group (CCG) initiated a trial for patients with infratentorial medulloblastomas and ependymonas. Patients, all of whom received post-operative cranio-spinal irradiation (CSI), were randomized to receive or not receive adjuvant chemotherapy (CT) with lomustine (CCNU), vincristine, and prednisone for 1 year. Thirty-six of the 42 patients with ependymoma entered on study were suitable for analysis; 22 received combined modality therapy and 14 irradiation (RT) alone. The failure-free survival (FFS) for the entire sample at 10 years is 36% and overall survival (OS) 39%, with no difference in outcomes between the two regimens. Survival was better for females (73%) than males (21%) and for those older than 10 years (51% vs. 31%). There were two toxic deaths in the group receiving CT. We conclude from this study with long-term follow-up that the CT used was not effective in improving the outcome in children with ependymoma.

Key words: CCNU, vincristine, childhood ependymoma

INTRODUCTION

In 1974, when the study reported here was designed, surgery plus irradiation (RT) was the treatment of choice for children with infratentorial ependymoma. There were reports that large field (tumor plus wide margins) RT had improved the 5-year survival from 20 to 40% [1,2]. For the higher grade infratentorial tumors, whole neuraxis RT was recommended because of the reported tendency to seed down the spinal cord [3,4]. Little information was available regarding any benefit of chemotherapy (CT). Because of the similarities between infratentorial ependymomas and medulloblastomas, it was decided that the ependymoma patients would be included as a subset within a study of medulloblastoma.

The Childrens Cancer Group (CCG) initiated a therapeutic trial (CCG-942) in 1975. Children with newly diagnosed posterior fossa medulloblastomas or ependymomas were eligible. The study compared cranio-spinal irradiation (CSI) alone versus CSI plus adjuvant lomustine (CCNU), vincristine, and prednisone. Both CCNU and vincristine had previously been shown to produce at least transient clinical improvement in children with recurrent brain tumors [5,6].

Prednisone was chosen for potential anti-tumor effects and to control possible peri-tumoral edema. The results of the medulloblastoma component of this study have been previously published [7]. This report gives the long-term, and therefore definitive, outcomes of the 36 eligible patients with posterior fossa ependymomas, a disease known to recur several years after primary treatment.

MATERIALS AND METHODS

Patients aged 2 to 16 years inclusive with newly diagnosed, previously untreated ependymomas were eligible for study if registered within three weeks following diagnostic surgery. Specifically excluded were those patients under 2 years of age, those more than three weeks following definitive surgery, those with post-operative bacterial meningitis, those with metastases beyond the neuraxis at diagnosis, and those with ependymomas arising outside the posterior fossa. Informed consent was obtained prior to randomization.

All patients initially underwent a neurosurgical procedure. Extensive tumor removal consistent with preservation of neurologic function was recommended in the pro-

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TABLE I. Staging System According to Chang et al. [8]

Stage	Description
T_1	Tumor <3 cm in diameter and limited to the classic midline position in the vermis, the roof of the fourth ventricle, and less frequently to the cerebellar hemispheres.
T_2	Tumor ⩾3 cm in diameter, further invading one adjacent structure or partially filling the fourth ventricle.
T_{3a}	Tumor further invading two adjacent structures or completely filling the fourth ventricle with extension into the aqueduct of Sylvius, foramen of Magendie, or foramen of Luschka, thus producing marked internal hydrocephalus.
T_{3b}	Tumor arising from the floor of the fourth ventricle or brain stem and filling the fourth ventricle.
T_4	Tumor further spreading through the aqueduct of Sylvius to involve the third ventricle or midbrain, or tumor extending to the upper cervical cord.
M_0	No evidence of gross subarachnoid or hematogenous metastasis.
M_1	Microscopic tumor cells found in cerebrospinal fluid.
M_2	Gross nodular seeding demonstrated in the cerebellar, cerebral subarachnoid space, or in the third or lateral ventricles.
M_3	Gross nodular seeding in spinal subarachnoid space.
M_4	Metastasis outside the cerebrospinal axis.

tocol. Extent of surgery was defined as: biopsy, partial resection (5 to 50% of tumor resected), sub-total (more than 50% and less than total), or total resection as estimated by the operating neurosurgeon. Patients with hydrocephalus requiring shunt placement were not excluded from the study. Pathology slides were reviewed centrally (at The Children's Hospital of Philadelphia), and all reported data are based on the central review diagnosis. Patients with a pathologic diagnosis of cellular or "benign" ependymoma, and anaplastic or "malignant" ependymoma, were eligible for study, but not those with ependymoblastoma (primitive neuroectodermal tumor with ependymal differentation).

Patients were staged according to the medulloblastoma Chang Classification (Table I), but were neither randomized nor stratified on this basis [8]. Neuroradiologic studies were to be performed at the treating physicians' discretion; computerized tomography was not generally available at the time of initiation of the trial. Myelography and cerebro-spinal fluid (CSF) cytology were not mandated, but strongly encouraged at the time of study entry.

Eligible patients were randomly assigned to receive either CSI alone (Regimen 2) or with adjuvant CT (Regimen 1). The end-point of the study was disease recurrence, as determined by the treating team's consensus. Abnormal symptoms in addition to new or progressive neurologic signs, or changes in radiographic studies, were necessary to diagnose disease progression. A determination of disease progression was made only after other causes of neurologic deterioration were excluded, e.g., hydrocephalus, steroid withdrawal, fever, anemia, post-irradiation somnolence syndrome, or electrolyte disturbances.

RT was to start as soon as possible following post-operative recovery, at the latest three weeks from definitive surgery. Standard RT of 35 to 40Gy to the entire cranio-spinal axis, plus a "boost" to the posterior fossa to a total dose of 50 to 55Gy, was to be delivered to all patients, except that reduction of 500 cGy to the posterior fossa for children under 3 years of age was suggested. Dose fractions of 160–200 cGy daily were recommended. The posterior fossa was to be irradiated using lateral parallel opposed fields at least 8 cm × 8 cm, with a minimum of 2 cm margin of normal tissue around the tumor in all directions. Tumor dose was defined as the central axis dose at the mid-plane of the opposed fields. Posterior fossa RT was to be delivered first, to be followed by the remainder of the neuraxis. Treatment was to be interrupted for an absolute neutrophil count (ANC) of less than 1,000 mm^3 and/or a platelet count of less than 75,000/mm^3. Institutional RT sheets were submitted for central review, but adequacy of the treatment volume could not be assessed, since neuro-radiologic studies and RT port films were not centrally reviewed.

Adjuvant CT for patients randomized to Regimen 1 consisted of vincristine 1.5 mg/M^2 (maximum dose of 2 mg) given by intravenous injection weekly for 8 weeks during RT. Following a 4-week rest period (i.e., 12 weeks from the start of RT), maintenance CT was to begin with cycles of 6-weeks' duration, consisting of CCNU (100 mg/M^2 orally on day 1), vincristine (1.5 mg/M^2 intravenously, maximum dose of 2 mg, on days 1, 8, and 15) and prednisone (40 mg/M^2/day orally, days 1 through 14, inclusive). Vincristine doses were to be omitted for severe neuro-toxicity (including constipation, weakness, seizures), then reinstituted at 50% of the original dose, with gradual increase to 100% as tolerated. The start of each CT cycle was to be delayed until the ANC reached 2,000/mm^3 and the platelet count greater than 100,000/mm^3. The CCNU dose was to be decreased for severe neutropenia and/or thrombocytopenia during any

TABLE II. Patient Characteristics

Characteristics	No. of patients	Treatment	No. of patients
Age			
1 to 4	15	XRT	14
5 to 9	11	XRT-Chemo	22
10+	10		
Sex		Resection	
Male	25	Partial	4
Female	11	Sub-total	24
		Total	8
Race			
White	23	Posterior fossa dose	
Black	4	Median: 5,090 cGy (range: 2,000 to 5,580)	
Other	8		
Unknown	1	Whole brain dose	
		Median: 3,600 cGy (range: 1,800 to 5,050)	
Stage			
T_1M_0	1	Spinal dose	
T_2M_0	2	Median: 3,600 cGy (range: 3,000 to 4,000)	
T_2M_1	1		
T_3M_0	22		
T_4M_0	8		
T_4M_3	2		
Brain stem			
Not involved	19		
Involved	15		
Unknown	2		
Shunt			
Yes	19		
No	15		
Unknown	2		

given cycle. Patients were to complete eight full cycles of CT.

Kaplan-Meier (life-table) estimates of survival and relapse-free survival were used throughout the analysis [9]. In this article, the term overall survival (OS) will be used in the statistical sense to denote the percentage of patients who are still alive at a specified time. Failure-Free Survival (FFS) will be used to denote the percentage who are alive without disease recurrence or progression. Tests of treatment effects and prognostic variables were based on the log-rank statistic and on the likelihood-ratio test based on Cox's multivariate regression model [10]. Follow-up for patients was that available through July 1992, the longest one being disease-free at 14 years.

RESULTS

From June 1, 1975 to June 1, 1981, 42 patients were entered on study with a diagnosis of ependymoma. As a result of the central pathology review, an additional patient with an institutional diagnosis of medulloblastoma was changed to ependymoma and added, while four patients with supra-tentorial tumors were removed as ineligible. The tumor pathology of three additional patients was not centrally reviewed and they are not included in this analysis. This was done to maintain histologic homogeneity within the study group. Thus 36 patients are evaluable, albeit four were entered non-randomly, two being treated with RT alone, and two treated with combined RT and CT.

Age at diagnosis ranged from 1 to 17 years, with a median of 5 years. (Although the protocol age range was 2 to 16 years, two infants of 1 year and one teenager of 17 years were entered on study and their results are included in this analysis.) There were 15 children (Table II) between 1 and 4 years of age, 11 children between 5 and 9 years; and 10 older than 10 years; the male to female ratio was 2.3:1, with 25 males and 11 females (Table II).

The length of follow-up for all evaluable patients ranged from 1 to 14 years with a median of 10 years. Three patients have been lost to follow-up and have been censored, disease-free, at 1, 3, and 4.5 years from study entry. The remaining patients have been followed for at least 8 years. There were two "toxic" deaths; both patients were treated on the CT arm. The first of these died of pneumococcal meningitis and septicemia while neutropenic at 16 months and the second of disseminated varicella while on therapy at 10 months, with no evidence of tumor at autopsy. There were no significant differences between the two treatment arms regarding clinical characteristics possibly affecting outcome such as age, sex, T or M stage, brain stem involvement, or extent of

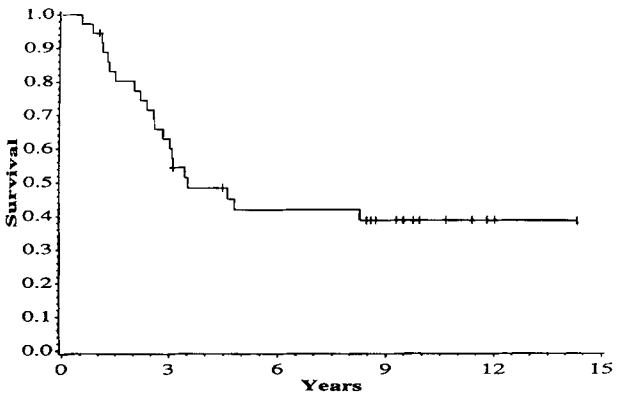

Fig. 1. Survival of 36 patients with 15 censored and 21 failed with a median of 3.5 years.

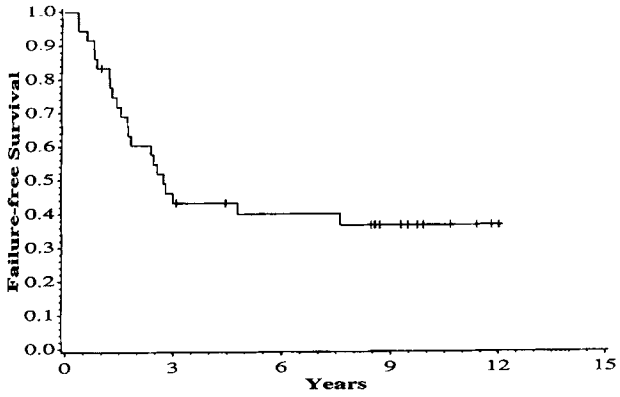

Fig. 2. Failure-Free Survival (FFS) with 14 censored patients and 22 failures with a median of 2.73 years.

resection, though Regimen 1 (RT + CT) had fewer patients 10 years and older than Regimen 2 (four of 22 versus six of 14).

OS and FFS of all patients are illustrated in Figures 1 and 2. Survival at 10 years is estimated to be 39% (95% confidence interval [CI] [22%, 55%]). FFS at 10 years is estimated to be 36% (95% CI [20%, 53%]). The difference between OS and FFS results from the long survival after recurrence of one patient. The median time to progression (MTTP) and median time to death following relapse (MTTD) are detailed in Table III for the total sample and the individual regimens. Twenty-two patients (61%) were treated with combined modality therapy (Regimen 1) and 14 (39%) with RT alone (Regimen 2). (This imbalance was caused in part by patients who were already assigned to one or the other regimen being eliminated or included on the basis of tumor site or histology.) There are no statistically significant differences in outcome between the two regimens. Ten-year survival for Regimen 1 patients is 40% and 35% for Regimen 2 (RT alone) (Fig. 3). There was no difference in the MTTP between the two regimens. A longer median time to death following relapse in the patients treated with RT alone (8 months compared with 3 months) does not reach statistical significance. Only three of 21 relapsing patients survived beyond 24 months from relapse (two after initial RT only, one after initial combined modality therapy). There were no distinctive characteristics separating these patients from the remainder of the study population that could be identified.

The 10-year survival was more favorable for females (73% vs. 21% [Table IV, Fig. 4.]). The outcome for patients less than 10 years of age at diagnosis was poorer than for those older than 10 (31% vs. 57% [Table IV, Fig. 5]). The difference achieves borderline significance ($P = 0.11$). This adverse impact of young age appeared distinct from advanced T stage, since larger tumors (i.e., Chang Stage T4) occurred similarly in older children (three of 10, 30%) compared with children less than 10 years of age (seven of 26, 27%).

Twenty-two of 36 patients (61%) on study were stage T3 at presentation, 10 (28%) were T4, three (8%) were T2, and one (3%) was T1. No interaction between T stage and outcome was observed. Myelography for M staging was not required in this study, and the total number of patients undergoing myelography and/or CSF cytology could not be determined from the available data. One patient was reported as M1 (tumor cells in the CSF) at diagnosis, and two were M3 (tumor seeding in the spinal subarachnoid space on myelography). All three patients subsequently experienced disease progression. (Institutions recorded M stage when the patient was registered on study but did not give CSF results in most M0 patients.)

The extent of resection, as judged by the operating neurosurgeon, could not be radiographically confirmed in this study which was initiated before widespread use of CT scans. However, eight were considered total resections, 24 sub-total, and four partial. An interaction between extent of resection and outcome could not be identified. Three of four (75%) patients with partial resections were disease-free, compared with eight of 24 (33%) and three of eight (38%) who had sub-total and total resections, respectively. Twenty-three percent and 20% of T3 and T4 tumors, respectively, were reported to have been totally resected.

There did not appear to be any prognostic significance between the identification of anaplastic or "malignant" ependymoma and cellular or benign ependymoma. Two of six (33%) of the malignant and 12 of 29 (41%) of the latter survive free of disease. A single patient labeled as "intermediate" grade II–III ependymoma has relapsed. There also was no difference in outcome between patients with low-grade ependymoma treated with RT alone (five of 12 or 42% FFS) or with combined modality therapy (seven of 17 or 41%). Five of six patients with "malignant" ependymoma were treated with combined modality

TABLE III. Outcome by Regimen

	Total study population	Regimen 1 Irradiation (RT) + chemotherapy (CT)	Regimen 2 Irradiation (RT) alone
Patient numbers	36	22	14
Overall survival (OS) at 10 years	39%	40%	35%
Failure-free survival (FFS)	36%	40%	29%
Median time to progression (MTTP)	18.4 months	17.1 months	20.6 months
Median time to death (after relapse) (MTTD)	3.1 months	2.5 months	7.6 months

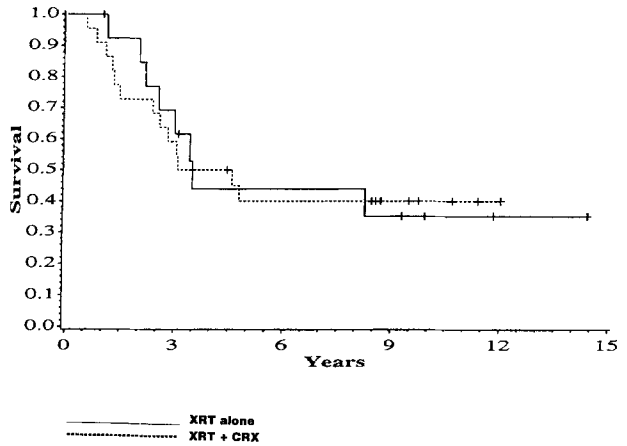

Fig. 3. Survival according to treatment. Regimen 1 (RT & CT): 22 patients, 9 censored, 13 failed, median 3.8 years. Regimen 2 (RT alone): 14 patients, 6 censored, 8 failed, median 3.5 years. Log Rank Test: $P = 0.93$.

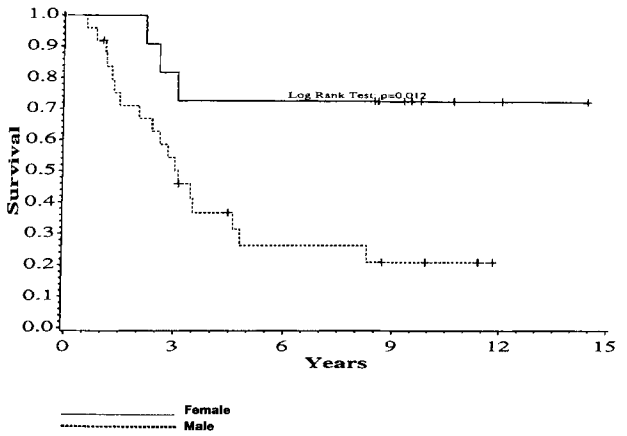

Fig. 4. Survival according to gender. Female: 11 patients, 8 censored, 3 failed, median not reached. Male: 25 patients, 7 censored, 18 failed, median 3.07 years. Log Rank Test: $P = 0.012$.

TABLE IV. Outcome by Sex and Age

	Median survival	Survival @ 10 yrs (%)	Figure
Sex			
Males	3.0	21	4
Females	not reached	73	
Age			
1 to 9	3.0	31	5
10+	not reached	57	

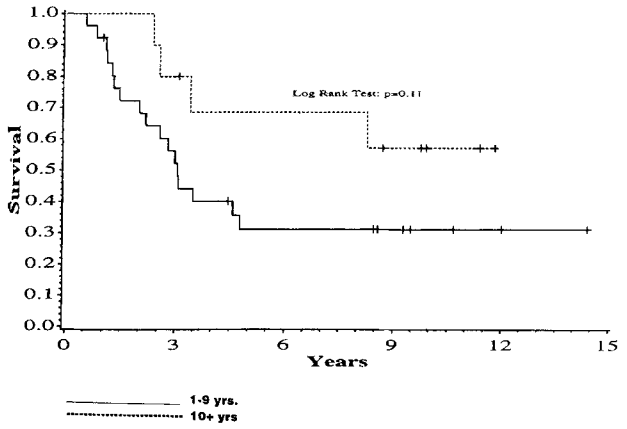

Fig. 5. Survival according to age. One to 9 years: 26 patients, 9 censored, 17 failed, median 3.05 years. Age 10 or more years: 10 patients, 6 censored, 4 failed, median not reached. Log Rank Test: $P = 0.11$.

therapy; four of six were 5 years of age or under at diagnosis.

The site of relapse was reported in 20 of 21 patients as posterior fossa; however, myelography was not routinely performed at relapse. One patient with a posterior fossa recurrence also had positive CSF cytology. A single patient had tumor cells in the CSF as the only evidence of tumor relapse.

Twenty-eight of 34 patients or 82% for whom RT doses are known, received between 50Gy and 55Gy to the posterior fossa and 14 (50%) of these remain disease-free. Two of four patients who received less than 50Gy have experienced progressive disease, as have both of the two given more than 55Gy. The apparent lack of association between higher RT dose and better local control could have been the result of a "geographic miss" and this possibility could not be checked since there was no central review of the treatment portals.

DISCUSSION

The original Childrens Cancer Group (CCG) randomized study for patients with medulloblastoma, initiated in

the mid-1970s, was designed to determine whether CT improved the outcome following surgical resection and RT. At that time, there was little information available regarding the benefits of CT for children with ependymoma, so they too were randomized as a subset of the same study. The agents chose, vincristine and lomustine (CCNU), were those that had been shown to produce responses in patients with medulloblastoma, and prednisone was added for its anti-edema effects.

This report is based on the 36 patients with infratentorial ependymomas whose histology was reviewed centrally. They were divided between those who received RT to the cranio-spinal axis alone and those who received RT plus the three drugs named. Treatment was assigned randomly in 32 and elected in four (evenly divided), who also are included in the analyses. The non-randomized patients were included in the analysis for completeness; exclusion of their data did not alter the conclusions of the study. The unbalanced randomization occurred by chance since ependymoma patients were included with those with medulloblastoma. Institutions with larger numbers of entries were randomized as a subset within the institution so it was possible that more ependymoma patients could be assigned to one area. It was also possible that a randomized patient could subsequently be excluded from study by the central pathology review. The FFS of the total group was 36%, without statistically significant differences in relapse-free survival or OS between the two regimens. There also were no differences when the patients were subdivided by regimen according to age, sex, radiation therapy dose, or degree of surgical resection.

Since the completion of this trial, there have been several studies of childhood ependymoma reported. Three of them (Nazar and colleagues [11], Goldwein and associates [12], and Healey and colleagues [13]) covered the same period as this study. None of the three, however, were designed to answer a CT question. The survival rates reported by them were 45, 46, and 61% at 5 years, and 46% at 10 years in the Healer et al. article, a result similar to the one reported here (39% at 10 years). All attribute a benefit of older age, but the definition of "older age" varied from over 2 to over 6 years, younger than the 10 years as defined in this analysis. The reason for the better outcome for the older patient is not obvious. We could not find any evidence that younger children had more extensive tumors, or received less treatment. An influence of age is seen in many pediatric malignancies in addition to medulloblastoma and ependymoma, such as Wilms' tumor and neuroblastoma, where young age is favorable, and ALL where it has an adverse impact. Contrary to the findings of Nazar et al. [11] and Sutton et al. [14], the extent of resection (or the surgical assessment of completeness of removal) did not affect our results. Healey et al. [13] points out that post-operative confirmation by radiologic imaging of a complete resection is a strong indicator of a favorable outcome. Such scanning was not available routinely in this study. The report of 93 adults by Vanuytsel and colleagues [15] with 5 to 10 year survival rates or 51 and 42% mentions the benefit of female gender, with 10-year survival values of 49% in females vs. 32% in males. Our findings showed a similar female advantage. Again, the reason for the better outcome for girls is not obvious but is striking, and confers a greater advantage with this disease than female gender does to patients with ALL.

It is of some interest to compare these results with those obtained in the medulloblastoma patients enrolled in the CCG-942. The 55% overall survival of medulloblastoma patients was better than that of the ependymoma patients. Again there was no significant difference between the results obtained after RT alone vs. RT plus the same CT employed. The adverse effect of young age seen in both ependymoma and medulloblastoma patients, was mitigated by CT in the medulloblastoma patients. No such improvement could be detected in the ependymoma sample, although the number available for analysis is small.

The results of this clinical trial mounted more than 15 years ago may seem disappointing. It must, however, be recalled that this report describes the outcomes of patients treated according to the best standards of surgery, radiotherapy, diagnostic radiology, and CT available at that time. It remains an important clinical trial because it demonstrated the feasibility of mounting a multi-institutional, multi-modal attack on childhood brain tumors. The study provided important information regarding the reasons for failure. The tumors recurred in the primary site, hence RT in the relatively high doses used does not appear to be adequate for local control. Also, the need for neuraxis RT can be questioned, as it has been by Goldwein et al.[12]. Furthermore, the drugs employed did not improve the outcome. Other chemotherapeutic agents (such as alkylating and platinum containing compounds) are being explored as adjuvant therapy, given the less than satisfactory results of local treatments.

CONCLUSION

This study reports the long-term outcome of a small group of ependymoma patients who were randomized to receive standard RT with or without the addition of CT. The agents prescribed—vincristine, CCNU, and prednisone—did not improve the survival rates. The study confirmed the better survival experience of girls and of children 10 or more years of age. No influence of histologic grade or extent or resection was seen, though the extent of resection was based on the operative findings and not on post-operative CT scans.

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